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EXAMINER	
JONES, D	
ART UNIT	**PAPER NUMBER**
1211	4

12M1/0930

DATE MAILED: 09/30/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-22 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☒ Claims 16 are allowed.

4. ☒ Claims 1-9, 14-15, 17, 19, 22 are rejected.

5. ☒ Claims 10-13, 18, 20-21 are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

103 REJECTION

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-9, 14-15, 17, 19, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner et al (R1: PTO 892), or Ryser et al (A& B: PTO 892).

Wagner et al (claims 1-4, 6-9, 17, and 22) discloses transferrin-polycation-conjugates useful as carriers for DNA uptake into cells. In particular, the nucleic acid delivery system involves conjugating the protein, transferrin to polycations that bind nucleic acids. The covalently linking of transferrin to the DNA protein, protamine, or to polylysines of various sizes occur through a disulfide linkage. In addition, the reference discloses: (1) the synthesis of the transferrin-polycation conjugates; (2) conjugation of transferrin with polylysine and protamine; (3) the formation of complexes between transferrin-polycation conjugates and DNA; and (4) the cell uptake and expression of luciferase gene resulting from the transferrin-polylysine and transferrin-protoamine conjugates mediating DNA uptake. However, Wagner et al fails to disclose examples wherein more than one polylysine is attached to the complex. But, it would have been obvious to a person of ordinary skill in the art at the time of the invention to make the necessary modifications to the transferrin-polycation-DNA complexes because Wagner et al discloses such complexes and suggests that typically, one polylysine moiety is linked to two transferrin

molecules, but the conjugation of more than one polylysine moiety is possible. The following sections of the reference should be examined, see entire document, especially, abstract; pages 3410-3411, "Synthesis of transferrin-polycation conjugates", "Conjugation of transferrin with polylysine", "Conjugation of transferrin with protoamine"; page 3411, "Synthesis of transferrin-polycation conjugates", "Formation of complexes between transferrin-polycation conjugates and DNA", Figure 1; pages 3412, "transferrin-polylysine and transferrin-protamine conjugates mediate uptake of DNA into cells and expression of a luciferase gene"; page 3413, "Discussion".

Both **Ryser et al** (claims 1-9, 14-15, 17, 19, and 22) disclose a method of effecting cellular uptake of molecules which are either excluded from the body or poorly transported into the cells. The molecules (i.e., informational macromolecules such as DNA or RNA) are covalently bonded to a cationic polymer which serves as a transport carrier to transport the molecules into the cells. The possible cationic polymers include polylysine and polyarginine which can be digested or otherwise broken down inside the cells after having served as transport carriers. In addition, Ryser et al discloses a conjugate formed between methotrexate and a cationic polymer which would enhance cellular uptake of methotrexate and carry the drug into methotrexate resistant tumor cells. However, Ryser et al fails to disclose examples wherein more than one polylysine is attached to the complex. But, it would have been obvious to a person of ordinary skill in the art at the time of the invention to make the necessary modifications to the transferrin-polycation-DNA complexes because the references suggest that through the use of a spacer molecule, covalently bonding methotrexate to other cationic polymers is possible. The

following sections of the references should be examined: (1) Ryser et al (A: PTO 892), see entire document, especially, abstract; columns 3-4, lines 65-68 and 1-18, respectively; column 4, lines 43-61; column 8, lines 23-51; columns 10-11, lines 50-68 and 1-49, respectively; column 17, Example 3; column 25, Example 13; column 39, Example 31; and (2) Ryser et al (B: PTO 892), the previously cited sections of Ryser et al (A: PTO 892) should also be reviewed for Ryser et al (B: PTO 892) because the disclosure for both patents is the same, they different only in what aspect of the invention is being claimed.

CLAIM OBJECTIONS

3. Claims 10-13, 18, and 20-21 are objected to as being dependent upon a rejected base claim, but would be allowable **over the art of record** if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

4. Claim 16 is free of the art of record.

5. Claims 10-13, 16, 18, and 20-21 are free of the art of record because the references cited above in the 103 rejection and those made of record on the PTO 892 do not suggest or provide the necessary motivation for one of ordinary skill to develop a delivery vehicle or a method of delivering a nucleic acid to a cell wherein the delivery vehicle contains a contrast agent consisting of a paramagnetic ion complexed with a chelator useful in magnetic resonance imaging..

6. The prior art made of record and not specifically relied upon in any rejections cited above is either: (a) considered cumulative to the prior art that was cited in a rejection; (b) considered pertinent to applicant's disclosure and shows the state of the art in its field but is not determined by the Examiner to read upon the invention currently being prosecuted in this application; or (c) was published after the applicant's filing or claimed priority date.

7. The processing of this application may be expedited by Applicant submitting drawings to be viewed by the Draftsperson since informal drawings were submitted by the Applicant.

8. Papers related to this application may be submitted to Group 1200 by facsimile transmission. Papers should be faxed to the Group 1200 fax machine at (703) 308-4556. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30; November 15, 1989.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dameron L. Jones whose telephone number is (703) 308-4640. Examiner Jones can generally be reached from Monday through Thursday, as well as on alternate Fridays, between 7:00 a.m. and 4:30 p.m. If the Examiner cannot be reached, questions may be addressed to her supervisor, John Kight, whose phone number is (703) 308-0204.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

JOHN KIGHT
SUPERVISORY PATENT EXAMINER
GROUP 1200

DLJ
September 17, 1996